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REVIEW ARTICLE

Environmental Tobacco Smoke: Current Assessment and Future Directions*

CARR J. SMITH, STEPHEN B. SEARS, JAMES C. WALKER, AND PATRICIA O. DELUCA

R. J. Reynolds Tobacco Company, Research & Development, Bowman Gray Technical Center, P.O. Box 1487, Winston-Salem, North Carolina 27102

ABSTRACT

Scientific information on environmental tobacco smoke (ETS) is critically reviewed. Key areas addressed are: differences in chemical composition between mainstream smoke, sidestream smoke, and ETS; techniques for measurement of ETS; epidemiology; *in vitro* and *in vivo* toxicology; and chamber and field studies of perceptual or physiological effects. Questions concerning estimation of ETS exposure, suitability of various biomarkers, calculation of lifetime dose, control of confounding variables, use of meta-analysis, and the relationship between ETS concentrations and human responses all emphasize the need for additional research in order to assess potential effects of ETS on health or comfort.

Keywords. Smoke chemistry; epidemiology; toxicology; sensory; measurement techniques; environmental tobacco smoke (ETS)

INTRODUCTION

Reports that nonsmokers experience acute and chronic health effects from tobacco smoke are relatively recent additions to the scientific literature. Reported acute effects include upper airway reactions as well as perceived odor and irritation. Epidemiology studies have reported associations between exposure to environmental tobacco smoke (ETS) and lung cancer, cardiovascular disease (CVD), and other respiratory diseases. In addition, a limited number of studies have been conducted on animals exposed to surrogate aerosols of ETS.

In 1980, White and Froeb (148) concluded that nonsmokers who were exposed to tobacco smoke in the workplace had significantly reduced small-airway function. In 1981, it was reported in 2 articles (63, 136) that nonsmoking wives of smokers were at increased risk of developing lung cancer. Studies reporting respiratory symptoms and assessing pulmonary function of children in smoking households date from the 1970s (27, 80, 122, 131). The first reports of studies to assess the relationship between exposure to tobacco smoke and cardiovascular disease in nonsmokers appeared in the 1970s (2, 70, 115).

The scientific literature on ETS has grown rapidly and today comprises thousands of articles. Reviews and assessments of these publications are also numerous, both in the US and internationally (33, 52, 72, 101, 138). Two reports produced in 1986 under federal government sponsorship concluded that ETS causes nonsmokers to have increased risk of lung cancer and increases respiratory infections and symptoms in children of smokers (101, 138). More recently, the Environmental Protection Agency issued a draft report estimating that 3,800 US lung cancer deaths per year are attributable to ETS (139).

Most of the research reported to date concerning ETS and health effects is from epidemiology studies. These individual epidemiology studies, however, have not provided a clear picture of relative risks associated with ETS exposure. The results are often inconsistent, and where there are reports of associations, those associations are very weak. Consequently, a variety of techniques, including meta-

* Address correspondence to: Dr. Stephen B. Sears, R. J. Reynolds Tobacco Company, Research and Development, Bowman Gray Technical Center, P.O. Box 1487, Winston-Salem, North Carolina 27102.

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TABLE I.—Diet and lung cancer risk.

Study	Dietary factor	Relative risk/odds ratio*
Fraser et al (44)	Low fruit consumption	3.83, $p = 0.0003$
Sakai (117)	Consuming the aloe plant	0.5, $p < 0.1$
Mettlin (98)	Consumption of whole milk	2.14
	Consumption of low-fat milk	0.54
Hole et al (66)	Low cholesterol level	Increased risk in those who smoke >15 cigarettes per day.
Connett et al (28)	Low serum beta-carotene	2.32
Marchand et al (91)	Low beta-carotene intake (men)	1.9 (95% C.I. 1.1–3.2)
	Low beta-carotene intake (women)	2.7 (95% C.I. 1.2–6.1)
Kune et al (78)	Serum beta-carotene Serum vitamin A	Patients had significantly lower levels than controls.
Koo (76)	Low fruit consumption	2.4, $p < 0.002$
	Low fish consumption	2.8, $p < 0.017$
Goodman et al (50)	High intake of cholesterol and fat	2.2 (95% C.I. 1.3–3.8) for men only
Pastorino et al (110)	Low plasma retinol	1.13
	Low retinol intake	3.27
	Low plasma beta-carotene	5.04
	Low beta-carotene intake	2.93
Bond et al (12)	Low vitamin A intake	2.0
Byers et al (16)	Low dietary fat intake	0.5
	Low fruit and vegetable consumption	1.8
Wynder et al (151)	Calories from dietary fat (by country)	Highly significant positive association ($p < 0.0001$) with national lung cancer mortality rate.
Menkes et al (97)	Low serum beta-carotene	4.30 (95% C.I. 1.38–13.41)
	Low serum vitamin E	2.5 ($p = 0.04$)
Pisani et al (112)	Low carrot consumption	2.9, $p < 0.01$ for current smokers
Chrisley et al (23)	Low vitamin B-6 level	All 12 cancer patients and none of the control subjects had vitamin B-6 inadequacy.
Ziegler et al (155)	Low carotene intake	1.4 (p-value for trend = 0.03) for squamous cell carcinoma.
Hinds et al (62)	Low vitamin A intake	2.0 (95% C.I. 1.2–3.5)
	Low carotene intake	2.2 (95% C.I. 1.3–3.7)
Byers et al (15)	High vitamin A intake	0.73 for squamous cell carcinoma

* For a complete description of the calculation of relative risks and odds ratios see Feinstein (39).

analysis, have been employed to evaluate these studies as a whole, in an attempt to provide greater statistical confidence in the findings.

This report briefly examines some of the difficulties in analyzing and interpreting the scientific literature on ETS and offers suggestions to overcome some of these limitations. In particular, it explores the following considerations:

1) In studying the hypothesis of an association between ETS exposure and the development of chronic disease, it is particularly difficult to account for confounding risk factors and the relative contribution of these factors.

Epidemiological studies of associations between ETS exposure and adult chronic disease have typically used the smoking status of household members as the index of exposure. The reported relative risks or odds ratios have generally been no larger than 2.0, approximately the same magnitude as confounding lifestyle factors (Tables I–IV). In addition, there is evidence that many of these confounders are non-symmetrically distributed between smoking and nonsmoking households (see Epidemiology section).

2) Significant chemical, physical, and physiological differences (e.g., component phase distribution, particle size, concentration, and inhalation/deposition patterns) between ETS, mainstream (MS) cigarette smoke, and freshly generated sidestream (SS) smoke preclude using MS or SS as simple surrogates for ETS. These differences also make evidence from studies exploring the effects of active smoking of limited value in drawing conclusions about ETS (51, 53).

3) Lifetime ETS dosimetry in a given nonsmoker is difficult to determine.

4) There is general agreement that meta-analytical techniques should follow certain established guidelines to increase confidence in the results. The lack of homogeneity within the reported ETS epidemiological studies renders meta-analysis problematic.

5) Sensory irritation associated with exaggerated ETS concentrations (10–100 times that found in field studies) does not provide a basis for drawing conclusions about the sensory effects of ETS at real world concentrations.

QUANTITATIVE DIFFERENCES BETWEEN ETS AND MS SMOKE

Laboratory research on ETS has been limited by the use of surrogate aerosols that are likely to have

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TABLE II.—Occupation and lung cancer risk.

Occupational exposure	Study	Relative risk/odds ratio
Welders	Breslow et al (13)	7.7
	Lerchen et al (84)	3.2 (95% C.I. 1.4–7.4)
	Buiatti et al (14)	2.8
	Tola et al (135)	7 observed, 2 expected ($p < 0.01$)
	Hull et al (68)	1.7 ($p < 0.05$)
Painters	Lerchen et al (84)	2.7 (95% C.I. 0.8–8.9)
	Engholm et al (37)	1.26
Painters, plasterers, and wallpaper hangers	Zahm et al (154)	2.0 (95% C.I. 1.2–3.3)
Farmers	McDuffie et al (95)	"Patients were consistently exposed more frequently to herbicides ($p = .05$), grains ($p < .015$), and diesel fuels ($p < .005$), and were consistently exposed to greater numbers of chemicals than were siblings ($p < .005$)."
Pesticide applicators	Vineis et al (140)	2.1 (95% C.I. 0.5–8.5)
Railroad workers exposed to diesel exhaust	Garshick et al (46)	1.45 (95% C.I. 1.11–1.89)
Chlorinated toluene workers	Sorahan and Cathcart (127)	1.80 ($p < 0.05$)
Chloromethyl ether workers	Maher and DeFonso (88)	2.79 ($p < 0.01$)
Steel workers exposed to acid mists	Beaumont et al (8)	2.00 (95% C.I. 1.06–3.78)
Pottery workers exposed to silica and talc	Thomas and Stewart (133)	3.64 among those exposed for 15 or more years.
Ceramic workers exposed to silica	Forastiere et al (43)	2.0 (95% C.I. 1.1–3.5)
Brick plant workers exposed to silica	Puntoni et al (114)	1.83
Asbestos	Sluis-Cremer and Bezuidenhout (126)	3.75
New Mexico uranium miners	Samet et al (120)	4.1 (95% C.I. 3.2–5.2)
Indoor radon	Samet (119)	"Estimates of the lung cancer risk associated with average lifetime radon exposure range from 0.1% to 1.0%."

different biological activities than ETS. A clear distinction should be made between mainstream (MS) cigarette smoke, sidestream (SS) smoke, and ETS.

ETS is the aged, diluted mixture of exhaled MS smoke and SS smoke. MS smoke, SS smoke, and ETS are largely composed of the same chemical compounds (4, 6, 35). However, because ETS is a highly diluted, dynamic mixture, it differs greatly from MS smoke and SS smoke in concentration, phase distribution, and component particle size (6, 51, 105).

The differences in phase distribution primarily result from 2 factors: the dilution (approximately 100–1,000 times) of ETS components, and differences in pH between MS smoke (below 7.0) and SS smoke (above 7.0). These physicochemical differences affect the volatility and phase transfer properties of ETS components.

The high degree of ETS dilution can be seen by comparing the concentration of individual MS components to the concentration of the same ETS components. These differences can approach 3 orders of magnitude (Table V).

In addition to phase and concentration differences, particle size differences between ETS, MS smoke, and SS smoke affect the bioavailability and therefore the biological activity of smoke components.

Relative humidity in the human respiratory tract approaches 100% (40, 51). In this environment, particles of freshly generated MS smoke increase in size because of coagulation and water acquisition. When exhaled, these enlarged particles (20–25% larger than the inhaled particles) almost immediately lose water and other volatile components to the atmosphere by evaporation. As a result, their size decreases.

TABLE III.—Genetic factors and lung cancer risk.

Genetic factor	Study	Relative risk/ odds ratio
Family history	Tokuhata and Lilienfeld (134)	2.7
	Ooi et al (108)	2.4
	Samet et al (118)	5.3
	McDuffie et al (96)	2.0
Rapid metabolism of the drug Debrisoquine	Ayesh et al (5) Caporaso et al (19)	4.5

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TABLE IV.—Poor lung function as a lung cancer risk factor.

Study	Risk factor
Kuller et al (77)	"Smokers in the lowest quintile of forced expiratory volume in one second (FEV_1) were seven times more likely to die of lung cancer than those in the highest two quintiles, $P \leq 0.001$ for linear trend."
Cohen et al (26)	After adjustment for age, sex, race, and smoking, the first-degree relatives of lung-cancer patients and of patients with chronic obstructive pulmonary disease were found to have significantly higher rates of impaired forced expiration than first-degree relatives of patients with non-pulmonary disease.
Guirgis et al (54)	These authors observed an increased frequency of pulmonary diseases in the relatives of lung cancer patients.

Note—peak lung function at maturity can be influenced by many factors, including: genetics, childhood respiratory infection, diet, exercise, premature birth, history of adult lung disease (pneumonia, tuberculosis), and environmental exposures.

Similarly, freshly generated SS particles—originally about the same size as freshly generated MS particles—also diminish in size as they lose volatile components, including nicotine, to the atmosphere. Through these evaporative processes, the mass mean aerodynamic diameter of SS particles formed during smolder is reduced 40–50% (71).

Measurements in active smokers have reported MS particle phase retentions ranging from 40% to 90% (61). When measured experimentally, ETS particle retention was found to be 11% (60).

MEASUREMENT TECHNIQUES FOR ETS

Accurately measuring ETS exposure is problematic. Various techniques have been evaluated and employed to measure ETS in an attempt to overcome the general difficulty of measuring minute concentrations of individual components in complex mixtures.

Chemical and biological estimates of ETS exposure have been reported. The most widely utilized chemical markers of ETS are nicotine and respirable suspended particulates (RSP). These components have been used to represent the vapor and particulate phases, respectively, of the ETS aerosol. Airborne nicotine, however, does not maintain a constant ratio to other vapor phase components (102). Furthermore, isolating ETS as a source of RSP is mitigated by the fact that other sources of particles are usually present. ETS typically contributes less than half of the total particles in indoor environments where smoking is allowed (34, 106, 113). Better chemical markers for ETS particle phase exposure that are under development include solanesol and ultraviolet particulate matter (106). 3-Ethenylpyridine is being investigated as a more precise indicator of vapor phase components (103).

TABLE V.—Dilution factors: MS components inhaled by a smoker versus ETS components inhaled by a nonsmoker breathing ETS-containing indoor air.

Tobacco smoke component	MS/ETS dilution factor
Nicotine	57,333–7,200,000
Acrolein	1,500–20,833
Benzene	112–7,167
Acetone	240–2,000
Benzo(a)pyrene	68–40,740

Data are taken from National Research Council data (101).

Biological markers that have been used to monitor exposure to ETS include carboxyhemoglobin in blood; urinary mutagenicity, as measured by the *Salmonella* assay; and concentrations of nicotine and a major metabolite, cotinine, in blood, urine, and saliva (56). In 1984, Matsukura et al (93) reported that cotinine could be used to indicate nonsmoker exposure to ETS. In 1989, Curvall (30) reported the use of trans-3'-hydroxycotinine as a more reliable indicator of ETS exposure than cotinine, but neither nicotine nor its metabolites can be used to quantitatively assess ETS exposure (104).

Further research is underway to establish biomarkers that are specific to tobacco smoke, reproducible, and proportional to the original concentration of ETS as a function of time. Currently, there are no accurate measures available to either chemically or biologically quantify ETS exposure.

EPIDEMIOLOGY

A number of challenges remain in order to perform reliable epidemiological studies of the potential association between ETS exposure and the development of chronic disease. These include improvements in lifetime dosimetry estimates and in adjustments for potential confounders.

Determining Lifetime ETS Exposure

A reliable lifetime exposure estimate is essential in studying the potential association between any compound and chronic disease. With the exception of certain acute respiratory conditions, the diseases that have been reported to be associated with ETS exposure are of a chronic nature and develop over a period of many years.

Several technical problems make estimates of lifetime ETS dosimetry difficult: 1) Current exposure is not necessarily a good indicator of past exposure. 2) Self-administered questionnaire and interview data are generally less reliable than biochemical measures of exposure. 3) Estimates of household

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exposure or workplace exposure do not consider other potential sources (e.g., bars, restaurants, etc.) of exposure that would alter the total dose.

Although it would be very difficult to overcome these technical problems in any epidemiological study, suggestions to partially address these difficulties include: 1) Analytical measurements of ambient ETS concentration should be taken in both the homes and the workplaces of cases and controls. 2) A reliable biological marker of ETS exposure should be measured from fluid or tissue samples taken from the subjects to confirm exposure. 3) Subjects should be interviewed, whenever possible, because data on past exposure are more reliable when collected by trained interviewers than by self-administered questionnaire (55, 87, 121). If the subject is not available, the subject's spouse is the relative of choice to interview.

Adjusting for Potential Confounders

Because the relative risks or odds ratios for human diseases reported to be associated with ETS exposure are typically no larger than the risks for confounding lifestyle factors, epidemiological studies of the association between exposure to ETS and chronic disease should be designed to maximize data quality and statistical power.

Several investigators have reported that smokers as a group have life-styles that put them at greater risk for chronic disease than nonsmokers, independent of smoking (36, 79, 124, 147). The life-styles of families of smokers and families of nonsmokers also differ. In 1987, Perusse et al (111) demonstrated familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. In 1989, Myers et al (100) reported results from the Framingham Study suggesting that there is a familial similarity in lipoprotein cholesterol levels.

Other authors have reported significant dietary differences between the families of smokers and the families of nonsmokers. Sidney et al (125) observed that the self-reported dietary intake of carotene is lower in nonsmokers exposed to ETS at home than in nonsmokers not exposed to ETS at home. These authors also found a higher proportion of current alcohol consumers and slightly higher mean body mass index in the exposed subgroup, despite its considerably lower age.

The ETS and chronic disease epidemiology studies conducted to date have not adequately controlled for all of the known confounding variables. When interpreting these studies, Angell's caveat (3) should be noted—"although there are statistical methods for neutralizing confounding variables, they are not perfect, and they are of no use whatsoever unless the confounding variables are known and measured."

ETS and Lung Cancer

At least 31 spousal studies have compared the risk of lung cancer in nonsmoking spouses of smokers to the risk in nonsmoking spouses of nonsmokers. These studies reported relative risks ranging from 0.7 to 2.55. Twenty-five of the studies reported no statistically significant increase in risk. On average, the 6 studies reporting an increase show an association generally less than 2.0 between spousal smoking status and lung cancer.

Although epidemiology studies do not establish causal relationships, the spousal studies do not make clear whether the reported associations are indicators of risk of ETS exposure, indicators of risk of spousal smoking status, or methodological artifacts. Because of inherent difficulties in interpreting any weak epidemiologic association and specific difficulties with the spousal studies, ETS/lung cancer epidemiology studies should contain the following elements: 1) Histological confirmation by a pathologist that the reported lung cancer cases are primary lung cancers. 2) Histological categorization of the primary lung cancer. 3) A "best estimate" of lifetime ETS exposure in cases and controls, taking into account factors mentioned earlier. 4) Demographic information concerning age, gender, ethnic origin, body mass index, etc. 5) Reliable estimates of the following reported lung cancer risk factors for both cases and controls: genetic predisposition as measured by family medical histories, air pollution, occupational carcinogens, long-term dietary habits, and peak lung function at maturity, exercise habits, prior lung disease (Tables I–IV).

ETS and Cardiovascular Disease (CVD)

To date, at least 10 epidemiology studies have examined the association between ETS and heart disease. Of the 4 studies conducted on men married to women who smoke, 3 (47, 83, 130) have 95% confidence intervals that go below 1.0. The 95% confidence interval of the fourth study (59) has a lower limit value of 1.1.

Of the 8 studies conducted on women married to men who smoke, 5 (45, 47, 64, 69, 83) have 95% confidence limits that either include or go below 1.0. The 95% confidence intervals of the other 3 studies approach 1.0, with lower limit values of 1.1 (59), 1.2 (92), and 1.3 (57). The 1 study that combined men and women (65) reported a 95% confidence interval with a lower limit of 1.2. All of these studies are either statistically insignificant at the 95% level or have lower limit values that approach 1.0.

Three studies (45, 47, 130) have reported positive

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associations (that were not significant at the 95% level) between exposure to ETS and CVD that are stronger than CVD risks reported in cigarette smokers (137). This anomalous result may suggest methodological problems with these studies.

Future biochemical epidemiology studies on exposure to ETS and cardiovascular disease should place greater emphasis on atherothrombotic, rather than just atherogenic, endpoints. Some degree of atherosclerosis is prevalent in males in Western societies, and atherothrombotic endpoints can be measured from blood samples and can be followed sequentially. Relevant atherothrombotic endpoints of interest in an ETS exposure study should include total peripheral white blood cell count, fibrinogen level, and possible indicators of platelet aggregation (32, 38, 74, 132).

Platelet aggregation has often been cited as a potential atherothrombotic event (74). The presence or absence of platelet aggregation after cigarette smoking can be experimentally determined, but its biological significance remains controversial. In addition, measurements of prostacyclin and thromboxane do not address whether the platelets of chronically smoke-exposed individuals are tolerant to chemical stimulators of aggregation.

ETS and Respiratory Health in Children

Hood et al (67) recently reviewed the epidemiological literature on ETS exposure and respiratory health in children. These authors stated:

> There appears to be a consistent association between parental (primarily maternal) smoking and respiratory symptoms and certain diseases in preschool children (44 reports). On the other hand, there is no consistent association between parental smoking and (1) respiratory symptoms or disease (46 reports); (2) middle ear disease (17 reports), (3) pulmonary function (38 reports), or (4) lung growth and development (5 reports) in school-age or older children.

An epidemiological association between ETS exposure and respiratory disease endpoints in children is difficult to determine because there are many possible factors in early lung impairment. Some factors that should be controlled in such an ETS epidemiology study include (94): 1) Mechanical trauma and hyperoxia on the premature lung (bronchopulmonary dysplasia). 2) Lung restriction that retards lung growth (pectus excavatum, congenital diaphragmatic hernia, congenital lobar emphysema). 3) Hypoxia that retards the subsequent structural and functional development of the pulmonary vasculature. 4) Airway inflammation in infancy that reduces subsequent airway function. 5) Maternal malnutrition or poor prenatal care during pregnancy. 6) Malnutrition during periods of rapid lung growth during infancy and early childhood.

In addition, such infectious exposures as measles, pertussis, adenovirus, etc., should also be determined in both the controls and the cohort under study. No study conducted to date has controlled for all of these risk factors.

As with lung cancer and heart disease, the differences in life-style between the families of smokers and the families of nonsmokers necessitate the consideration of potential confounders when investigating childhood respiratory disease. The socioeconomic status of the household and cross-infections from parents and siblings are particularly difficult to disentangle in these studies of acute effects.

ETS and Respiratory Health in Adults

Respiratory diseases and symptoms in either healthy or compromised adults exposed to ETS have not been as widely studied as in children. No clear picture emerges from an analysis of the approximately 40 published papers on this subject, because the literature reports positive and negative associations as well as nonassociations.

The ETS studies on adult respiratory health are influenced by many of the same potential confounders as the childhood studies, but there are at least 5 factors that may be of increased importance in considering design of ETS studies in adult populations: 1) Presence of adult lifestyle confounders (e.g., alcohol consumption, caffeine consumption, hobbies such as woodworking and ceramics, etc.). 2) Occupational exposures to lung irritants. 3) Difficulty in obtaining accurate lifetime medical histories. 4) Greater difficulty in estimating current and past ETS exposure because of the increased mobility of adults. 5) Increased possibility of psychological aversion to ETS, resulting in exacerbation of reported symptoms.

In vitro Studies on ETS

In vitro techniques have been used for many years to assess the mutagenicity and cytotoxicity of compounds and complex mixtures. There may be no consistent correlation between the carcinogenicity of a chemical compound in animal tests and positive genotoxic or cytotoxic *in vitro* results (1). Nonetheless, valuable mechanistic information can sometimes be obtained from the results of these tests.

Recently, the biological activity of ETS was assessed using a cellular smoke exposure technique that utilized exposures to ETS of 1.5 mg/m^3, approximately a 15-fold increase over real-life measured levels of RSP, of which ETS comprises at most 50% (11). Effects of this ETS concentration were

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compared to those of room air. ETS was not cytotoxic (neutral red assay), mutagenic (Ames tests using the TA98 strain with S9 metabolic activation) or clastogenic (sister chromatid exchanges).

Animal Studies on ETS

Several nose-only inhalation exposure studies of MS smoke have reported histopathological changes of the respiratory tract and related organs in several species.

A 14-day inhalation study in rats was recently conducted to determine whether ETS would produce similar results (24). This study used SS smoke that was aged and diluted (ADSS) to closely approximate the phase distribution and concentrations of ETS components. Animals were exposed nose-only, inside whole-body chambers, to ADSS from the 1R4F reference cigarette. Endpoints included histopathology, CO-oximetry, plasma nicotine and cotinine, clinical pathology, and organ and body weights. The only pathological response observed was slight to mild epithelial hyperplasia and inflammation in the most rostral part of the nasal cavity, in the high exposure (100× "real-life") group only. No effects were noted at medium (10×) or low (1×) exposures. The minimal changes noted were reversible.

A 90-day study by Coggins et al (25) using the same ADSS concentrations produced similar results, with no histopathological progression noted. In addition, no new histopathological changes were observed at 90 days. These results are in agreement with von Meyerinck et al (141), who conducted a 90-day SS smoke study on rats and hamsters utilizing an exposure of 4.0 mg/m^3 in which the only histopathological changes observed were reversible hyperplasia and metaplasia of the epithelium covering the dorsal nasal turbinates in the rats.

Lee et al (81) examined DNA adducts and alveolar macrophage cytogenetics in the rats from the 14-day inhalation study conducted by Coggins et al (24). Exposure-related adducts were not observed in any of the animals at 0.1 or 1.0 mg/m^3; these figures represent ambient and a 10-fold exaggeration for measured ETS concentrations, respectively. Slight diagonal radioactive zones, characteristic of adducts observed in animals in smoke exposure studies, were observed, but only in lung and heart DNA of animals exposed to the highest concentration of ADSS (10 mg/m^3), a 100-fold exaggeration of typical field measurements of ETS. No elevation in chromosomal aberrations was observed in the alveolar macrophages. These results are consistent with the histopathology data in support of a no-observed-effect-level (NOEL) of 1.0 mg/m^3.

Meta-analysis

Meta-analysis is a collection of statistical procedures for combining and analyzing data from "similar" studies. It is contrasted with primary analysis (the original analysis of data from a single study) and secondary analysis (the re-analysis of original data by a different technique, for another purpose or by another investigator) (48).

Most often, meta-analysis operates on summary statistics of primary studies—correlation coefficients, *p*-values, relative risks, or contingency tables—as opposed to a pooled compilation of raw data from individual studies (58). Meta-analysis is almost exclusively applied to derive a single consolidating statistic that represents the significance of an intervention effect (e.g., symptom remediation under a prescribed treatment regimen) or to derive a relative risk for exposure to a particular agent (128).

Sacks et al (116) have cited the following objectives of meta-analysis: 1) to increase statistical power for primary endpoints and for subgroups, 2) to resolve uncertainty when reports disagree, 3) to improve estimates of effect size, 4) to answer questions not posed at the start of individual trials.

Several researchers have provided guidelines for proper application of meta-analytic techniques (10, 22, 42, 73, 109, 116, 152, 153). The guidelines of Sacks et al (116), as presented by Fleiss and Gross (42), are paraphrased below:

Study Design

The design of the meta-analysis should include a protocol prepared before study initiation. The protocol should describe the purpose of the meta-analysis, the methods for obtaining published data, a list of all studies found, criteria for exclusion of studies not pooled in the meta-analysis, and summary data on clinical and demographic characteristics in the studies.

Combinability

Researchers should report their criteria for whether individual studies are sufficiently "similar" to be combined. This includes the calculation of a statistical homogeneity/heterogeneity index.

Control and Measurement of Potential Bias

One important potential source of bias in meta-analysis is the selection of the studies that are included. Selection or rejection should be based on the methodology of the studies (not on their results). Bias may also arise in extracting data from individual studies. To minimize "extraction bias," 2 or more investigators should independently review the studies and attempt to reach consensus. Sources of

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funding for the meta-analysis should also be identified.

Statistical Analysis

An appropriate statistic for averaging "within-study" differences (analysis of variance or Mantel-Haenszel) should be employed. Point and interval estimates, in addition to overall significance tests, should be reported. The question of statistical power should be addressed, especially when a weak or insignificant association is predicted by the meta-analysis. Subgroup associations hypothesized *a priori* should be meta-analyzed (i.e., the decision to study specific subgroups should be made before the results of the full meta-analysis are known).

Sensitivity Analysis

Studies should be analyzed in more than 1 way (different statistical tests, assumptions, or criteria) to confirm qualitative agreement. The potential impact of publication bias (the rejection by publishers of studies that fail to show an effect) and "the file-drawer phenomenon" (the tendency of authors to not submit for publication studies that fail to show an effect) should be carefully assessed. The quality of the individual studies should be assessed (weighted) and incorporated in the final conclusions.

Application of Results

Once the pooled statistics have been obtained, the investigators should carefully evaluate the results for procedural rigor and overall validity, questioning whether a definitive answer has been provided, or whether further studies are needed.

Some authors have also emphasized the following: 1) the importance of including only randomized studies in a meta-analysis (153), 2) the value of displaying data graphically (10, 42), 3) the importance of searching both the published (peer-reviewed) and unpublished (theses, regulatory documents, etc.) literature for data (10, 153). In addition, the quality of the meta-analysis cannot exceed the quality of the component data sets.

Meta-analysis has recently been applied to the epidemiology of lung cancer in relation to ETS (9, 42, 85, 86, 101, 139, 142, 146). These meta-analyses were based on a variety of assumptions and corrections, and they used different protocols, subject populations (overlapping to various extents), and meta-analytic tools.

All meta-analyses found summary risk ratios less than 2.0 (most less than 1.5) for nonsmoking women married to smokers. All meta-analyses used at least 1 of the 2 procedures developed by Mantel and Haenszel (90) or Yusuf et al (153). Letzel and Uberla (86) used both procedures, in addition to Fisher's p-value method (41).

The meta-analyses of the National Research Council (NRC) (101), the Environmental Protection Agency (EPA) (139), Wald et al (142), Wells (146) and Blot and Fraumeni (9) predicted lower 95% confidence limits above unity, indicating statistical significance for increased risk. The lower confidence limits of Letzel et al (85) and Fleiss and Gross (42) were below unity, indicating nonsignificantly increased risk.

All relative risks calculated were small (150). The fragility of such small increased risks (89) indicates the need for statistical power analyses and further epidemiology (42).

Many questions remain about meta-analytic theory and application (21, 42, 49, 116, 128). Most practitioners of meta-analysis question the propriety of combining studies of widely variable study populations, methodologies and controls.

Among the more important questions raised by meta-analysis of ETS studies are how to account for variances in the quality and size of component data sets, how to correct for publication bias, how to account for potentially confounding variables in the individual and overall statistics (42), and how to assess the overall homogeneity/heterogeneity of studies.

Misclassification bias has also been suggested as a potential source of error in ETS epidemiology (82). Finally, Fleiss and Gross (42) stress the need for data adjustment for misclassification of case-control status and exposure level.

Short-term Effects of ETS Exposure

Background

ETS may have both perceptual and reflexive effects in nonsmokers. Nonsmokers may perceive odor, nasal irritation, and eye irritation; in some cases, they may also see ETS. Reflexive responses that have at least been anecdotally associated with ETS include increased eye blinking, tearing, runny nose, cough, headache, and upper airway changes such as bronchoconstriction. All of these effects are influenced by both the smoke concentration and individual differences in sensitivity to ETS.

Although information on the prevalence of any of these effects in work or any other environment is scant, some laboratory experiments on responses to ETS have been reported. These can be divided into those that emphasize perceptual effects and those that deal primarily with physiological or pharmacological measurements of upper airway function.

Perceptual Studies

In a number of studies reported in the past 10–12 years, ratings of odor and irritation were measured over ranges of concentrations of true ETS or

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machine-generated SS smoke. In several of these studies, the nonsmokers were also asked to rate the annoyance from, or acceptability of, chamber air after smoke was produced. Most often, carbon monoxide (CO) concentrations were used as a measure of smoke concentration. Estimates of the smoke concentrations used in these studies, relative to those found in actual smoking environments, may be made by comparing the average nicotine and RSP concentrations reported in a series of recent field-sampling studies (20, 29, 107) with those measured in a recent laboratory study (143). This comparison indicates that ETS concentrations corresponding to elevations of ~0.15–0.30 ppm CO might be representative of office and restaurant smoking environments. Because all reports of the perception of ETS employed concentrations much higher than this, these studies provide an incomplete understanding of the perceptual effects from environmentally realistic exposures. Nonetheless, several findings from this line of research are worthy of note:

1) With combinations of smoking and ventilation rates that result in CO concentrations of 2 ppm or lower, 90% of chamber occupants report being satisfied with the air; at 5 ppm CO, satisfaction declines to 75% (18).

2) Filtration to remove particulate matter from SS smoke at 10 ppm CO greatly reduces ratings of perceived eye or nasal irritation (144). Relatively smaller declines in odor and irritation were seen with particulate matter removal at lower (2 and 5 ppm CO) concentrations of ETS (18).

3) Eye blink rate and changes in respiratory behavior are of little value as physiological correlates of perceived irritation in nonsmokers exposed to environmentally realistic levels of ETS. Both measures are largely unaffected unless concentrations at least 20-fold higher than real world levels are employed (75, 99, 143–145).

4) Prolonged exposure (at least 30 minutes) to constant ETS concentrations of 1.3–10 ppm CO results in gradual increases in perceived eye and nasal irritation (18, 99).

5) The single most sensitive measure of ETS annoyance, particularly at lower concentrations, is odor. There is some evidence that the intensity, rather than the quality, of the odor is the more important determinant of nonsmokers' annoyance (17).

The research by Cain et al (17, 18) that indicated a key role of odor in ETS complaints, employed ETS concentrations in the range of 2–5 ppm CO. When lower concentrations, more closely approximating those in office smoking environments, are presented in future studies, one would expect the relative importance of odor to increase substantially. Considerations of the meaning of nasal or eye irritation ratings should await the collection of data at these lower concentrations. Ideally, future studies in this area should also determine the ETS concentration thresholds for odor, irritation, and more "global" measures such as annoyance or acceptability.

Studies of Upper Respiratory Reactions to ETS

Attempts to produce asthmatic responses or other changes in upper airway function in nonsmokers have used concentrations of machine-generated SS smoke in the range of 8.7 (129) to 50 (149) ppm CO and have produced equivocal results. In 14 asthmatics (4 of whom reported that ETS aggravated their symptoms), SS smoke concentrations of approximately 24 ppm CO did not alter forced expiratory volume in 1 second (FEV_1) or maximal expiratory flow rate at 50% of vital capacity ($\dot{V}max50$) (123). Wiedemann et al (149) exposed 9 asthmatics (6 of whom reported that ETS "bothered" their asthma) to SS smoke concentrations corresponding to 40–50 ppm CO. These exposures did not result in changes in FEV_1 or $\dot{V}max50$, but they did produce a 2% decrease in forced vital capacity (FVC). A slight *decrease* in nonspecific bronchial reactivity (measured via methacholine bronchoprovocation) was also reported. Dahms et al (31) reported decreases of 21.4 and 20%, respectively, in FEV_1 and FVC in 10 asthmatic patients (5 of whom reported that ETS exacerbated their asthmatic symptoms) when exposed to calculated SS smoke concentrations of 15–20 ppm CO. Stankus et al (129) tested 21 asthmatics who reported that their symptoms were exacerbated by ETS. Fourteen subjects showed no response to SS smoke concentrations as high as 13.3 ppm CO. Of the remaining 7 subjects, 2 showed a decline of at least 20% in FEV_1 with an 8.7 ppm CO exposure and 5 required a concentration of 13.3 ppm CO to exhibit the same response.

Some research into the possible effects of smoke on inflammatory or allergic responses in the nasal cavity has been reported recently. Bascom et al (7) found no evidence for an allergic response to SS smoke concentrations corresponding to 45 ppm CO. Rhinorrhea symptoms and increased nasal resistance were reported in subjects who considered themselves "ETS-sensitive" at this same concentration.

As with the laboratory studies of sensory responses to ETS, the need for research into the possible upper airway effects of ETS at concentrations in the range of those encountered in actual smoking environments is apparent.

Conclusion

Although the scientific literature concerning ETS and its association to human health continues to

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grow at a dramatic pace, the difficulty in interpreting the results of these studies leaves many important questions unanswered. Moreover, results from scientific studies conducted to date do not sufficiently support conclusions concerning health effects that might be associated with exposure to ETS. Additional research would prove fruitful in this regard.

Basic questions concerning reliable estimates of ETS exposure, the appropriateness of various biomarkers, the calculation of lifetime dosimetry, the control of confounding factors, the use of meta-analysis, and the relationship between ETS concentrations and human sensory perceptions emphasize the need for additional investigation before conclusions about potential effects of ETS on health or comfort can be made.

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CRITIQUE

Justice, Science, and the "Bad Guys"

When accused of a new offense, does someone regarded as a "bad guy" have the right to due process and a fair trial? If such a right is inherent in the legal systems of civilized society, is it also a part of justice in the "courts" of scientific evaluation? I ask these questions because, in private conversation, I recently heard an authoritative leader in the world of public health epidemiology make the following statement: "Yes, it's rotten science, but it's in a worthy cause. It will help us get rid of cigarettes and become a smoke-free society."

The statement, of course, referred to the data and evaluations assembled in the past few years for accusations about what is formally called *environmental tobacco smoke* and informally designated as *passive smoking*. According to the accusations, this type of exposure causes at least 2 of the prime evils hitherto attributed to direct smoking: lung cancer and cardiovascular disease. In fact, several of the recent cardiovascular studies found risks that were even higher for passive smokers than for direct smokers. (The authors tactfully refrained, however, from stating the implicit conclusion that people who cannot avoid passive exposure should lower their risk by beginning to smoke directly.)

A new part of the current indictment is the claim that passive smoking is responsible for respiratory and otologic difficulties in children. Because young children so rarely engage in direct smoking, pediatricians have hitherto had little participation in the research industry devoted to studying cigarettes. Now, with open hunting season declared on the effects of passive smoking in children, a fertile new opportunity has arisen for selfless public service, fame, grants, and publications.

Nevertheless, if the science is as "rotten" as the public health authority admitted, does the end really justify the means? If objectivity, precautions against bias, and careful operating guidelines are essential for a "bad guy" to get fair treatment in a court of law, should those principles be abandoned or abolished when the "bad guy" is in a court of science?

A peripheral inspection, without any in-depth appraisals, of the current accusations about passive smoking would suggest that many scientific principles have vanished. I shall cite 3 overt examples:

1) Many of the pediatric researchers seem unaware of the frequent disparity between symptoms and objective evidence of ailments whenever people are passively exposed to a "bad guy." Perhaps the most striking demonstration of this phenomenon

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A peripheral inspection, without any in-depth appraisals, of the current accusations about passive smoking would suggest that many scientific principles have vanished. I shall cite 3 overt examples:

1) Many of the pediatric researchers seem unaware of the frequent disparity between symptoms and objective evidence of ailments whenever people are passively exposed to a "bad guy." Perhaps the most striking demonstration of this phenomenon

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occurred in a classic and scientifically superb epidemiologic field investigation on "Subjective Fears and Objective Data." In that landmark study, Spitzer et al (4) showed the excessive frequency with which residents of a Canadian community, exposed to "sour gas" fumes from a nearby mine, complained of diverse ocular, respiratory, neurologic, and other symptoms for which no objective pathology could be found. In an analogous control community elsewhere, where residents were exposed to the same degree of emissions but where their evils had not been publicized, the prevalence of analogous symptoms was substantially lower. Nevertheless, no attention seems to have been given to this phenomenon when symptoms were evaluated for children exposed to the presumptive evil of passive smoking.

2) In meta-analyses of passive smoking studies, as recently pointed out by Fleiss and Gross (2), the investigators have complied with almost none of the scientific guidelines established for this type of research. While agglomerating masses of data obtained *without* randomized trials, the meta-analysts have also given little or no attention to the frequently stated guideline that randomization is a *sine qua non* for the scientific credibility of a meta-analysis.

3) A fundamental rule in criteria for causality is that the evidence from different studies consistently goes in the same direction. This consistency in different investigations of *direct* smoking was one of the key supports in the Surgeon General's Committee's original decision (5) to label cigarettes as a "bad guy." In the investigations of *passive* smoking, however, the various studies are contradictory, some going in positive directions and others not. The inconvenient failure of the evidence to comply with a prime requisite of scientific reasoning for causality, however, has not inhibited the causal accusations. The "prosecution" has simply ignored the inconvenient results and emphasized those that are (in a memorable term) "helpful."

Aside from the problems of getting a fair trial in a court of law, does a "bad guy" also have the right to get a lawyer? If this principle is also a traditional bulwark in systems of justice, what kind of "lawyer" will be available in scientific courts if the act of defending a "bad guy" is almost universally regarded as depraved and immoral? For example, in the current fervor of anti-smoking evangelism, what young scientists would want to risk their careers and what older scientists would want to risk their reputations by doing anything that might be construed as support for the "bad guys" of the tobacco industry? What governmental agency would fund research in which the established "accepted" anti-smoking doctrines were threatened by a study proposed by someone—an obviously deranged skeptic—who wanted to do an unbiased, objective investigation?

The governmental agencies that fund scientific research were once expected to be above the battle, uncommitted, and devoted to seeking truth, however it might be found. For diverse political, social, and fiscal reasons, however, those agencies have often in recent years become mechanisms of advocacy rather than scholarship, pursuing goals of policy rather than science.

Any organization that is under attack—a governmental agency, a foundation, a university, a political group, even a profit-making industry—is always given the right to defend itself by getting a "lawyer," who is usually called a "consultant." This right is apparently also denied to the tobacco "bad guys." Like any other group under attack, the "bad guys" would like to get a respectable, competent consultant—in this instance, an academic or federal investigator of impeccable credentials, who has never been tainted by anything other than federal grants, and who is preferably so disinterested as to believe perhaps that Philip Morris signed the Declaration of Independence and that R.J. Reynolds manufactures aluminum. In the current atmosphere, however, the consultant's stature, credibility, and integrity become instantly impugned and tarnished by the depravity of associating with the tobacco "bad guy."

Another interesting principle is that no one seems troubled when a "good guy" does things that are feared as the behavior of a "bad guy." For example, the National Institutes of Health (NIH) regularly conducts "consensus conferences" in which the main goal is a press release and published document intended to impress Congress into larger allocation of research funds. The assembled participants for these conferences are usually investigators beholden to the NIH for grants (or hopeful of getting them). No one complains that the methods exemplify poor science; the goals and morals are serene, laudable, worthy. No one seems troubled when a federal agency exercises tight censorship over the work of its grantees, as in later years of the Framingham epidemiologic study. Yet large outcries of immorality arise when an investigator doing pure research in basic human biology accepts funds from the Tobacco Industry, given with no strings, no censorship, and complete scientific liberty to pursue the work wherever it leads.

In such an atmosphere, "bad guys" who believe they are getting a "bum rap" will defend themselves as best they can. There thus appears, in this issue of this journal, a review of passive smoking written by four people (3) who have the worst possible background for scientific acceptability. They are not even

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"hired-gun" outside consultants; they are actually directly employed by the tobacco industry.

Many readers will adamantly refuse even to examine a report from such sources. The few who actually begin reading will probably do so with clenched teeth and firm preconceptions. Nevertheless, if science depends on evidence and reasoning, rather than on the sponsoring source, the report is a fascinating document. Expecting a partisan polemic, I found it surprisingly even-handed, well constructed, and well written. It is certainly much better in all these respects than analogous documents prepared by the allegedly disinterested and dispassionate evaluators at governmental agencies. In fact, if the report by Smith et al (3) were published anonymously, with no identification of the authors or their employer, it might well be lauded as an excellent or even model review of the topic.

Instead, however, what the authors have prepared will probably be instantly dismissed because it comes from the "bad guys," and because they failed to do the self-immolation that would have gained approval in the scientific policies of the current status quo. Beyond the authors' sin of engaging in rational self-defense, the editor of this journal will probably be pilloried for publishing the report, and I expect my own share of slings and arrows for failing to castigate it and for even hinting that it may be a worthwhile scientific document.

If public health and epidemiology want to avoid becoming a branch of politics rather than science, the key issues are methods and process (1) not the "goodness" of the goals or investigators. In science even more than law, the "bad guy" (often appearing as a *counter-hypothesis, paradigm shift,* or *skeptical evaluation*) should always have the right to state his case, and a well-stated case has the right to be heard, regardless of who pays for it.

Besides, the "bad guys" sometimes turn out to be correct. Galileo was assailed by the Church when he doubted Earth's centrality in the solar system; Semmelweis was denounced by obstetricians when he said their inadequately cleansed hands were transmitting disease; Florence Nightingale was detested by the British establishment when she campaigned for better sanitation of water and sewage; and Joseph Goldberger was deemed a fanatical nuisance when he questioned an esteemed epidemiologic commission's report that pellagra was an infectious disease.

Just as "bad guys" are sometimes right, the "good guys" are sometimes wrong. The history of medicine and public health is replete with the errors (sometimes harmful blunders) committed by revered, respectable leaders in the field. The most recent memorable public events were the unnecessary, fallacious hysteria about the hazards of Agent Orange, and the needless evacuation of homes (and harm to lives) by residents of an entire town in Missouri, responding to the mistaken zeal of a governmental agency.

The "bad guys," of course, are not always right, but if they are denied a fair and proper scientific hearing, neither society nor science will benefit. Society is entitled to make political decisions based on advocacy. The scientific basis for those decisions, however, should depend not on political advocacy, but on scholarship—no matter how it is produced or by whom.

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Discussant: Alvan R. Feinstein
Sterling Professor of Medicine and Epidemiology
Yale University School of Medicine

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